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The impact of diagnosis by legionella urinary antigen test on the epidemiology and outcomes of Legionnaires' disease

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SUMMARY

Legionnaires' disease is an uncommon but important cause of life-threatening community-acquired or nosocomial pneumonia. The urinary antigen enzyme immunoassay test, used in Victoria since 1995, now accounts for the majority of initial laboratory notifications (81% in 1999). We review the impact of the test on the disease epidemiology and the public health investigative process. We focus on the major subgroup of cases due to *Legionella pneumophila* serogroup 1, comparing delays until notification and mortality for urinary antigen detected cases with culture detected cases. The urinary antigen test facilitates a 5-day reduction for the delay between onset of illness and notification. We observed that there was minimal clinical heterogeneity of urinary antigen detected cases whether they were subsequently culture confirmed or not. We encourage clinician use of the urinary antigen test in cases of community-acquired pneumonia where Legionnaires' disease is a possible diagnosis, in conjunction with culture of clinical specimens.

INTRODUCTION

Legionnaires' disease is an important cause of severe community-acquired and nosocomial pneumonia, with studies in Europe and North America showing that legionella infection is responsible for 1–5% of all hospitalized community-acquired pneumonia cases [1–3]. One Australian study reported *Legionella* species as causing 3% of hospitalized cases of community-acquired pneumonia [4]. The case fatality rate for Legionnaires' disease for hospitalized patients remains quite high with rates of 5–30% reported, depending on the underlying risk factors of the patients [5].

In all states of Australia, Legionnaires' disease is a notifiable disease, with national notification rates of about 1/100000 population (unpublished observations). *Legionella pneumophila* species are the most common cause of Legionnaires' disease in Victoria. Most outbreaks of Legionnaires' disease in Australia have been due to *Legionella pneumophila* serogroup 1 (LP1) [6–12].

The definitive method for laboratory diagnosis of Legionnaires' disease remains culture of *Legionella* species on selective media [13]. Other diagnostic methods in routine use in Victorian laboratories include serological testing by immunofluoresence, and the Binax legionella urinary antigen enzyme immunoassay. Detection methods using nucleic acid amplification are not routinely recommended in Victoria.

The Binax urinary antigen text (UAT) detects antigens from *Legionella pneumophila* serogroup 1 (LP1), and is reported to be highly specific and

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sensitive [14]. A major advantage of the UAT is that results are rapidly available compared to culture or seroconversion. UAT results can be available within 24 h, whereas positive culture results may take in excess of 6 days, and seroconversion on convalescent serum may not be demonstrated for weeks.

In 1998 we undertook to review the utility of the UAT on the public health investigative process for Legionnaires' disease following our favourable experiences with the test in outbreaks. The UAT has been used in Victoria since September 1995. It had been anecdotally observed that the majority of notifications were now based on a positive UAT result.

METHODS

Case definition

The criteria for notification of Legionnaires' disease in Victoria are: a clinically compatible illness (pneumonia) and at least one of the following: (1) culture isolation of *Legionella* species; (2) fourfold rise in immunofluoresence (IFA) titre in paired sera to at least 128; (3) stable high titre (>512) IFA in convalescent serum; (4) demonstration of *Legionella* species antigens in urine or other specimens [15].

Follow-up of notifications

In Victoria, investigation of notified cases of Legionnaires' disease are co-ordinated by the Communicable Disease Section of the Department of Human Services (DHS). Standardized telephone questionnaires are completed through interviews of cases, relatives and treating doctors. The questionnaires collect information about basic case demographics and possible risk factors for legionella infection in the 10-day period prior to the onset of illness. The Environmental Health Unit of DHS assess potential sources of legionella infection in consultation with the Communicable Disease Section.

Review of public health files of notifications

We performed a sequential case series analysis on public health investigative files for all notifications of Legionnaires' disease in Victoria by onset date of illness, for the period 1995–9, establishing a study database using EpiInfo Version 6.18.

For the first part of the analysis we summarized information on the *Legionella* species responsible for disease, diagnostic results and demographic features of all notifications of Legionnaires' disease.

For the second part of the analysis we reviewed all laboratory confirmed cases of LP1 that were first detected by either UAT or culture. We did not include serologically diagnosed cases for comparison since these notifications did not usually represent notifications received in the acute stage of illness, and we were primarily interested in consideration of the timeliness of UAT compared to culture detected cases.

We defined the delay in notification as the period in days from the date of onset of illness until receipt of a notification. Comparison of median delays in notification between detection by UAT or culture were performed using EpiInfo Version 6.

We compared case demographics for cases detected by culture compared to those detected by UAT, and further subdivided UAT detected cases to those with and without subsequent confirmation by either culture or serology. The rationale for such a division was to begin to explore what difference may exist between UAT detected cases which are later confirmed by other tests, compared to those without subsequent confirmation.

Other sources of data

Additional information about the UAT utilization was obtained from the Victorian Infectious Diseases Reference Laboratory (VIDRL). This public health reference laboratory performs a large proportion of urinary antigen testing in Victoria, but the test is also performed by some private pathology providers. UAT test utilization for those private providers are not available.

RESULTS

Case series analysis of all cases of Legionnaires' disease

We analysed 212 public health investigative case files with date of onset of illness between 1 January 1995 and 31 December 1999.

Legionella species responsible for disease

Legionella pneumophila serogroup 1 has been responsible for the majority of notified cases of Legionnaires' disease in Victoria during the study period (median proportion of all notifications 82%: annual range 75–91%). Other notified *Legionella*

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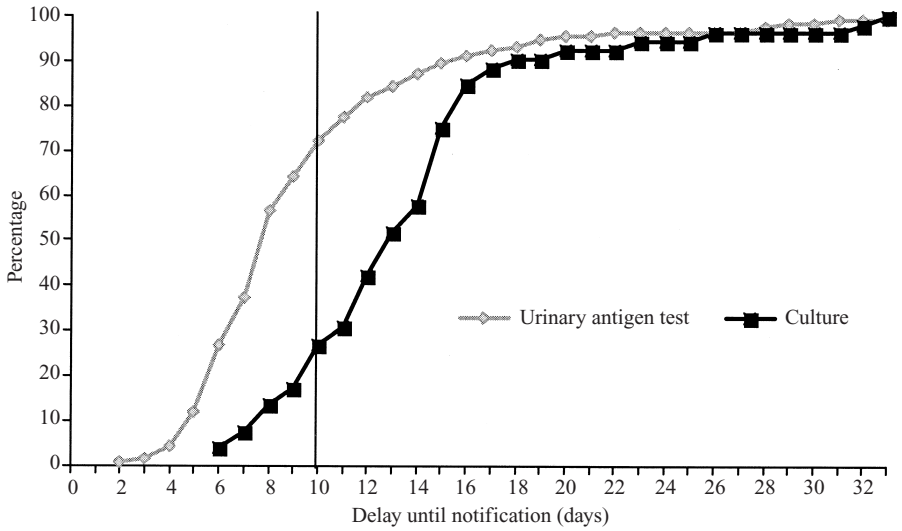

Fig. 1. Cumulative frequency distribution of the delay until notification (in days) for 167 cases of Legionnaires' disease due to *Legionella pneumophila* serogroup 1 diagnosed by culture ($n = 52$) or urinary antigen test ($n = 115$) in Victoria, 1995–9.

species included *Legionella longbeachae* 11/212 (5% of all notifications) and *Legionella micdadei* 8/212 (4% of all notifications). Small numbers of non-serogroup 1 *Legionella pneumophila* were also reported (6% of all notifications).

Twenty-three cases of LP1 were associated with two outbreaks in 1998. Small numbers of clusters of less than five cases of LP1 were investigated in other years. Other *Legionella* species and serogroups were not associated with outbreaks or cluster investigations.

Diagnostic results

A progressive increase has occurred in the proportion of diagnoses of Legionnaires' disease detected by UAT since 1995. UAT detected diagnoses increased from 5% of all notifications in 1995, to 81% of all notifications in 1999. For the same period, there has been a large increase in UAT utilization at VIDRL. Overall UAT utilization at VIDRL has increased from ten tests in 1995, to 1532 tests in 1999.

Case demographic features

Most cases are aged between 40 and 70 years (74%), and there are proportionally more females than males in older age groups compared to younger age groups. The male/female ratio is 3·7 for this study period. Smoking status was recorded for 174/212 (82%) of cases. 119/174 (68%) of these cases were reported as smokers, although the duration and frequency of tobacco use is not known.

The median proportion of fatal cases for the period 1995–9 was 12% (annual range 5–21%). The majority of cases were hospitalized, with the median proportion of cases hospitalized being 96% (annual range 94–8%). There was more variability in the proportion of cases requiring ventilation in an intensive care unit (median 53%: annual range 21–68%).

Cases of Legionnaires' disease due to *Legionella pneumophila* serogroup 1 (LP1) detected by urinary antigen test or culture

We identified 167/212 (79%) of all cases as LP1 detected by either culture ($n = 52$), or UAT ($n = 115$) for this study period.

Timeliness of notification

The median delay until notification is 13 days (range 6–33 days) for culture detected cases, and 8 days (range 2–79 days) for the UAT detected cases (Wilcoxon rank sum test for non-normally distributed data: $z = 5{\cdot}64$; $P < 0{\cdot}0001$). Within 10 days from the onset of illness, 72% of cases detected by UAT are notified compared with 27% of cases detected by culture (Fig. 1).

The time delay until notification can be subdivided using the date of collection of diagnostic specimens. For 71/115 (62%) of LP1 cases detected by UAT, there was a median delay of 6 days from illness onset until urine collection (range 1–31 days). Seventy-three percent of cases had urine collected within a week of illness onset. This compares with a median delay of 8

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Table 1. *Characteristics of 167 Legionnaires' disease notifications due to LP1 1995–9, by culture or UAT detection*

Characteristic	Culture ($n = 52$)	Urinary antigen test ($n = 115$)	UAT alone ($n = 70$)	UAT with later confirmation ($n = 45$)	Total ($n = 167$)
% male	85	77	81	71	80
Median age in years (with range)	57·6 (26·1 – 84·6)	55·3 (27·5 – 92·8)	57·3 (27·5 – 92·8)	52·4 (27·6 – 84·7)	55·8 (26·1 – 92·8)
% hospitalized	98	97	97	98	98
% ventilated in Intensive care unit	81*	32	19‡	53	47
% fatal cases	25†	8	6	11	13

* Statistically significantly higher proportion at 5% level for culture detected compared to all UAT detected ($P < 0{\cdot}0001$).
† Statistically significantly higher proportion at 5% level for culture detected compared to all UAT detected ($P = 0{\cdot}002$).
‡ Statistically significantly lower proportion at 5% level for UAT alone detected compared to UAT with later confirmation ($P < 0{\cdot}001$).
Other comparisons non-statistically significant at 5% level.

days from illness onset until respiratory specimens collection for 32/52 (62%) of cases detected by culture (range 3–25 days). Only 47% of these culture detected cases had respiratory specimens collected within 1 week of onset of illness.

Case demographic features

A positive urinary antigen result was followed by a positive culture isolate in 44/115 (38%) of cases. The median additional delay from notification by the UAT until culture notification, was 7 days (range 0–21 days) for 28/44 (64%) of these cases. A single UAT diagnosed case had subsequent serological confirmation but not culture confirmation. Table 1 presents comparative demographic data for LP1 cases diagnosed by culture, cases diagnosed by UAT alone, and cases diagnosed initially by UAT with later confirmation by either culture or serology.

DISCUSSION

Since the UAT has been introduced in Victoria, there is evidence of public health benefits through use of the test. There is a shorter median delay until notification for LP1 cases detected using the UAT compared to culture. The notification for a case diagnosed by the UAT is received up to 5 days earlier than that of a culture confirmed case. From subdividing this delay, it appears that the 5-day period gained is a combination of time gains from earlier collection of diagnostic specimens (2 days), and for the testing process until a notification is received by public health authorities (3 days).

Earlier case notification may facilitate an earlier public health response. This can lead to earlier identification of outbreaks and implementation of outbreak measures. These outbreak measures can lead to harm minimization through case prevention or early case identification and treatment. Earlier notification of sporadic cases may lead to identification/control of potential environmental sources and thus prevention of further cases.

We observed that culture detected LP1 cases (compared to UAT detected cases), were statistically significantly more likely to be fatal cases or cases ventilated in intensive care. There were not significant differences in hospitalization rates or the age/sex distribution. To properly address what may account for these observed associations, a range of potential confounding variables would need to be considered. These include treatment details (especially the delay until appropriate antibiotic therapy), pre-morbidity of cases, age/sex distribution, smoking history and immunosuppression.

We were not able to obtain adequate information about clinical treatment from the public health case files to perform an adjusted mortality analysis, and lacked resources to collect the data from the clinical files located mainly at hospitals across the state. One factor which we believe needs to be considered as an important confounder is the fact that if patients are intubated, it is then easier to obtain higher quality respiratory specimens, which may result in higher

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culture confirmation rates for intubated patients. Since these patients are sicker, it would be expected that fatality rates for this group would also be higher.

We observed that at least 38% of UAT detected LP1 cases had subsequent culture confirmation. This proportion is likely to be an under-estimate of the proportion subsequently culture confirmed, since not all laboratories may be attuned to the public health importance of notification of subsequent culture confirmation to public health authorities. We also do not know what proportion of UAT detected cases do not have adequate culture specimens collected, or if specimens are collected some time after antimicrobial therapy has commenced.

We are not able to comment on the features of cases from the entire series that were culture positive but urinary antigen negative, due to incomplete data. However, we have reported elsewhere a subset of the cases we investigated in detail during an outbreak [11]. Urine specimens collected in the first week after onset of illness were sometimes UAT negative in culture confirmed cases.

We compared case demographics for UAT detected cases for that group that were subsequently culture confirmed, to those that were not culture confirmed. From the variables we analysed, we did not find evidence that LP1 identified by UAT alone formed a group that was clinically heterogenous to the group of UAT detected cases subsequently culture confirmed. We noted differences in the proportion of cases intubated in intensive care, for which we have previously postulated an explanation.

This demonstrated lack of clinical heterogeneity provides supportive evidence to the argument that UAT detected cases without subsequent culture confirmation are likely to be true positive cases. To provide stronger evidence, more detailed comparisons of clinical heterogeneity using clinical case files are needed.

It is important to note that the UAT is not an alternative to culture and serology. The major limitation of the test remains its validity being limited to diagnose cases due to LP1 only. Therefore we recommend that culture and serology specimens are also routinely collected. Culture isolates from cases are also of critical importance to public health investigations by allowing comparisons with environmental isolates through molecular sub-typing procedures. Culture and serology remain important first-line investigations, especially in areas where LP1 causes a smaller proportion of cases than in Victoria.

We encourage clinicians to use the UAT in areas with a high proportion of cases of Legionnaires' disease due to LP1, since there is a clear potential to facilitate an earlier public health response in both sporadic case investigation and in outbreak settings. The presence of a strong collaboration between public health authorities, public health laboratories and the clinical sector facilitates the usefulness of the UAT in optimizing public health outcomes.

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